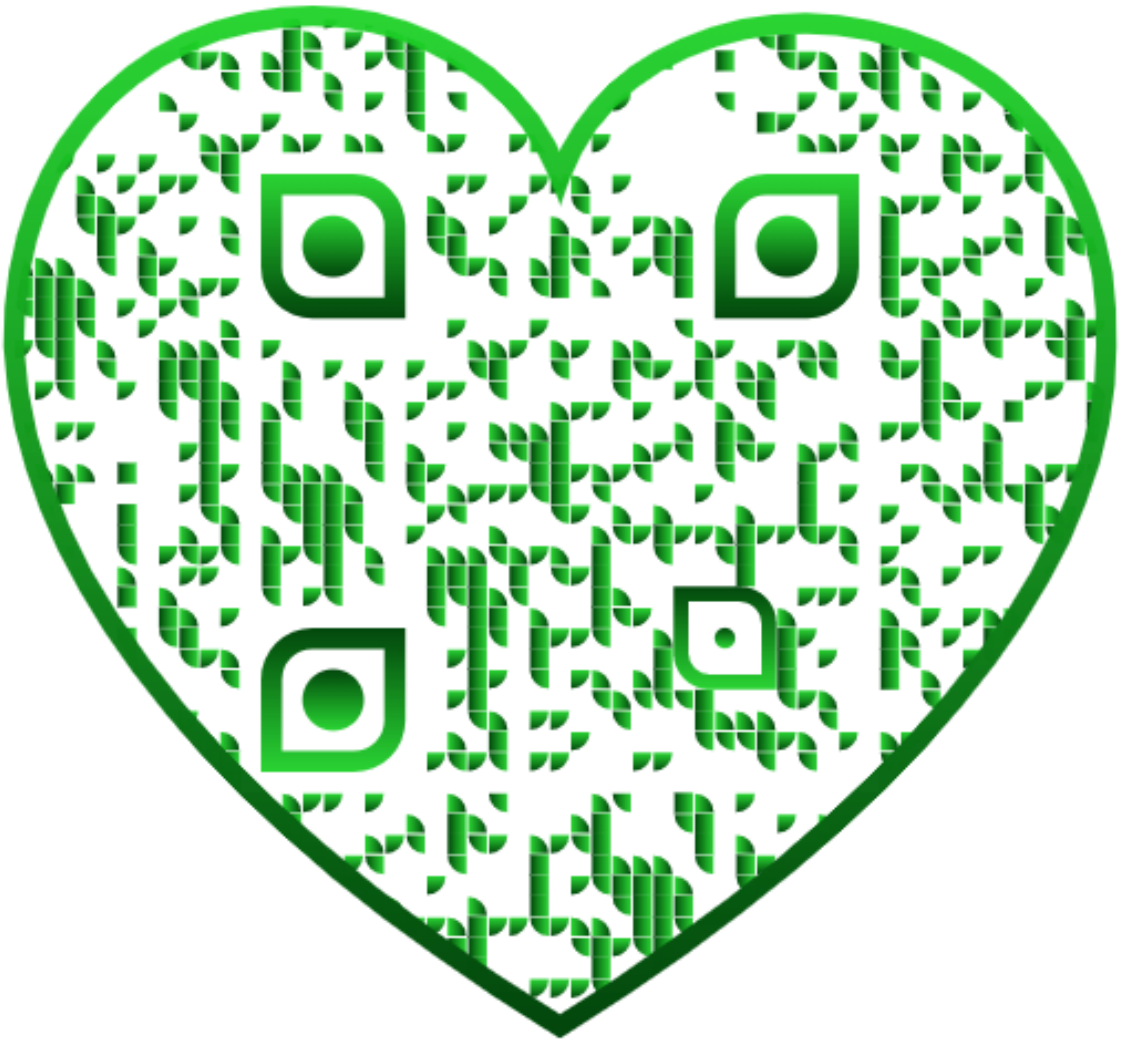
2. Basic Pharmacokinetics

1. Order and rate constants
2. Pharmacokinetic models
3. Non-linear pharmacokinetics
4. Drug ADME
5. PK of IV bolus injection
6. PK of constant rate infusion
7. PK of extravascular dose
8. Dosage regimen



2.1 Order and Rate constants

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- After a drug is administered, it is subjected to a number of processes (ADME).
- The **rates** of these processes
  - Control the concentration of drug at the site of action.
  - Affect the **onset, duration,** and **intensity** pharmacological response.

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- The **rate** of a reaction or process is defined as the **velocity** at which it proceeds and can be described reaction orders.
    - Zero order*
    - First order*
    - Second order
    - Third order …

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- In the equation,

$$-\frac{dY}{dt} = K_n Y^n$$

  - $\frac{dY}{dt}$ represents **rate** of the process.
  - The numerical value (n) of the exponent of the substance (Y) is the **order** of the process.
  - K is the rate constant.

Zero-order process

- Where n = 0 in the rate equation $-\frac{dY}{dt} = K_n Y^n$
- Since $Y^0 = 1$, $-\frac{dY}{dt} = K_0 Y^0$ will be written as $-\frac{dY}{dt} = K_0$

Where, K_0 the zero-order rate constant (mg h^{-1}).

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- The reaction proceeds at a constant rate and is **independent** of the concentration of Y present in the body.
  - E.g. elimination of alcohol.
- The integration of the zero-order rate equation will yield:

$$Y = Y_0 - K_0 t$$

where Y is amount present at time t and Y_0 is amount at time zero.

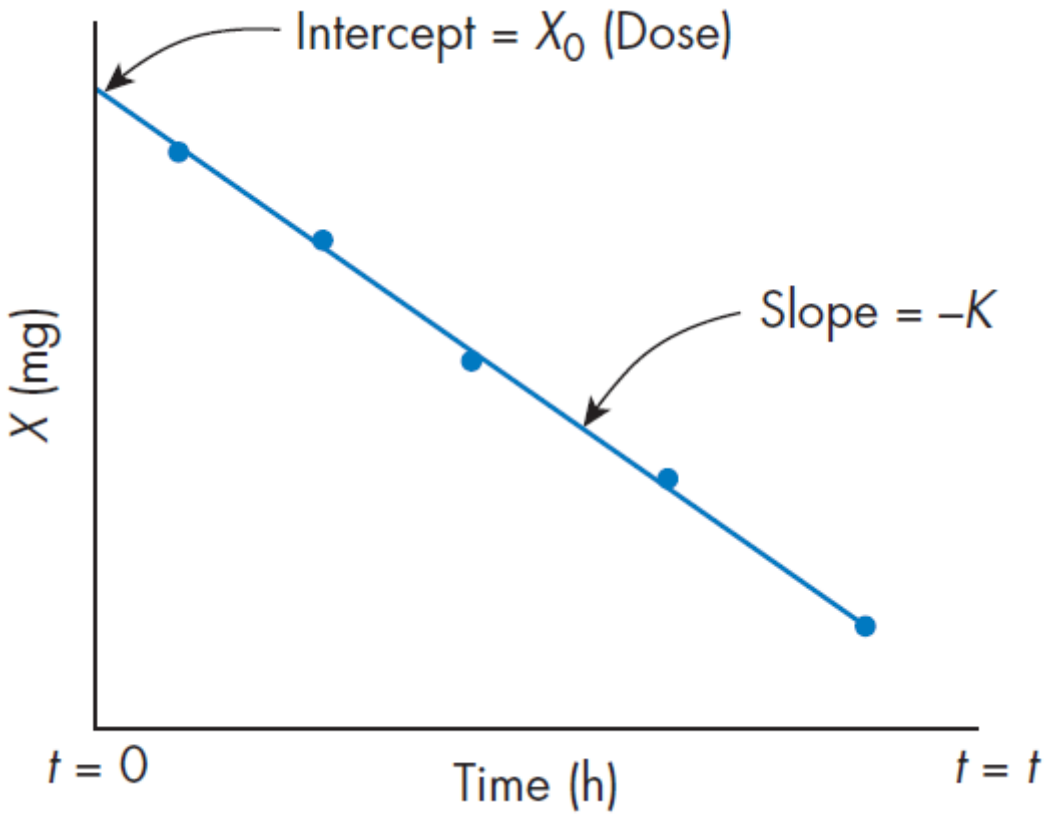

Fig. Zero-order process (X, concentration of drug; K, rate constant)

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- Applications of zero-order processes include:
    - Intravenous infusion
    - Release from controlled release dosage forms
    - Transdermal drug delivery systems

First-order process

- Where n = 1 in the rate equation $-\frac{dY}{dt} = K_n Y^n$
- Since $Y^1 = Y$, $-\frac{dY}{dt} = K_1 Y$

  Where, K_1 the first-order rate constant (h^{-1}).

- The reaction proceeds at a constant rate and is dependent of the concentration of Y present in the body.
  - E.g. the rate of elimination of most drugs

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- The integration of the first-order rate equation will yield:

$$Y = Y_0 e^{-Kt}$$

or $$\ln Y = \ln Y_0 - Kt$$

or $$\log Y = \log Y_0 - Kt/2.303$$

where Y is amount present at time t and Y_0 is amount at time zero.

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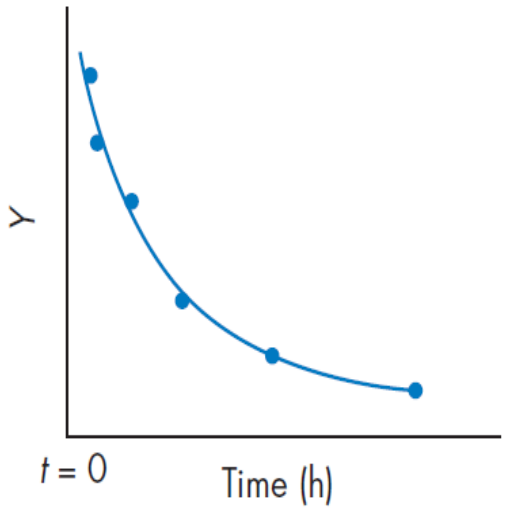

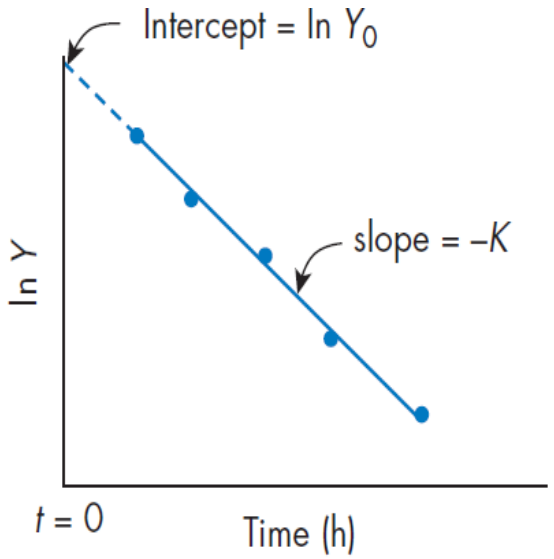

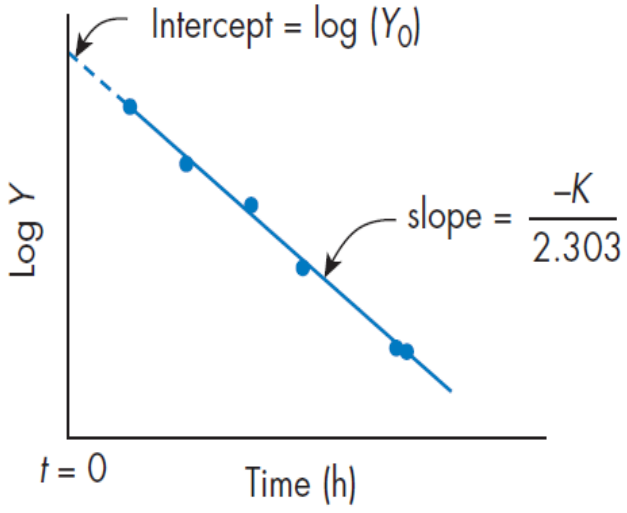

$Y = Y_0e^{-Kt}$

$\ln Y = \ln Y_0 - Kt$

$\log Y = \log Y_0 - Kt/2.303$

2.2 Pharmacokinetic models

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- PK models are hypothetical structures used to describe the fate of a drug in a biological system following its administration.
- Various mathematical models can be devised to simulate the rate processes of drug ADME.
- Useful in the development of **equations** to describe drug concentrations in the body as a function of time.

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- Pharmacokinetic models are divided into:

    1. Compartmental models
    2. Physiologic (perfusion) models
    3. Model independent methods (statistical moment theory)

- The most useful model is the **compartment model**.

Compartmental models

- **Compartment** ~ an entity which can be described by a definite volume and a concentration of drug contained in that volume.
  - In a PK analysis of data, the living system is conceived to be composed of a number of mathematically interconnected compartments.
    - Between which drug moves and from which elimination occurs.
    - The transfer of drug between these compartments is represented by rate constants.

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- Properties of a classical PK compartment:
  - Kinetic homogeneity,
  - Drug concentrations within a compartment depends on the partitioning and binding properties of the drug,
  - Within each compartment, distribution is immediate and rapidly reversible,
  - The barriers between compartments are considered diffusion rate limiting,

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- Distribution to any tissue within a compartment depends upon blood flow, blood volume, and partitioning, as well as tissue and plasma protein binding,
- Compartments are interconnected by first-order rate constants,
- Input and exit rate constants may be zero order.

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- Depending on the degree of vascularity and distribution pattern of the drug, two compartment models:

  A. Central compartment

  B. Peripheral compartment

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- **Central compartment**
  - All body regions (organs and tissues) in which the drug concentration is in instantaneous equilibrium with that in blood or plasma.
  - Drugs in circulating fluids (plasma) and rapidly perfused tissues (e.g., heart, liver, kidney, lungs) are assigned to the central compartment.

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- **Peripheral compartment**
  - All body regions (organs, tissues) to which a drug eventually distributes, but not in instantaneous equilibrium.
  - Drugs in fluids of distribution (i.e., lymph and extracellular water) and poorly perfused tissues (e.g., large muscle mass, skin, and the central nervous system) are assigned to the peripheral compartment.

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- On occasions, the kinetics of a drug may follow a three compartment model for which the peripheral compartments represent "**shallow**" and "**deep**" compartments.
  - The deep compartment is considered less accessible than the shallow compartment.
  - A shallow compartment ~ the skin, muscles, the CNS etc.
  - A deep compartment ~ teeth, bone, hair, nails, or cartilage (e.g., accumulation of tetracycline derivatives in bone).

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- The compartment model is utilized in PK to estimate selected fundamental PK parameters such as:
  - The apparent volume of drug distribution (V_d),
  - The elimination half life ($t_{1/2}$) and
  - The elimination rate constant (K) of a drug.
- These parameters allow for the calculation of the **dosage regimen**.

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- The selection of a compartment model solely depends upon the distribution characteristics of a drug following its administration.
  - If the drug is **rapidly** distributed, a one-compartment model will be adequate to accurately and adequately characterize the (C_p vs t) data.
  - The terms rapid and slow distribution refer to the time required to attain distribution equilibrium for the drug in the body.
  - All organs and tissues behave in similar fashion toward the administered drug.

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- **Slow** distribution suggests that the distribution equilibrium is attained slowly and at a finite time.
  - It suggests that the vasculature, tissues and organs are not behaving in a similar fashion toward this drug.
  - We consider the body to comprise two compartments or, if necessary, more than two compartments.

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- The model selection process is highly dependent upon the following factors:

1. The frequency at which plasma samples are collected.

    - It is highly recommended that plasma samples are collected as early as possible following the administration of the dose of a drug.

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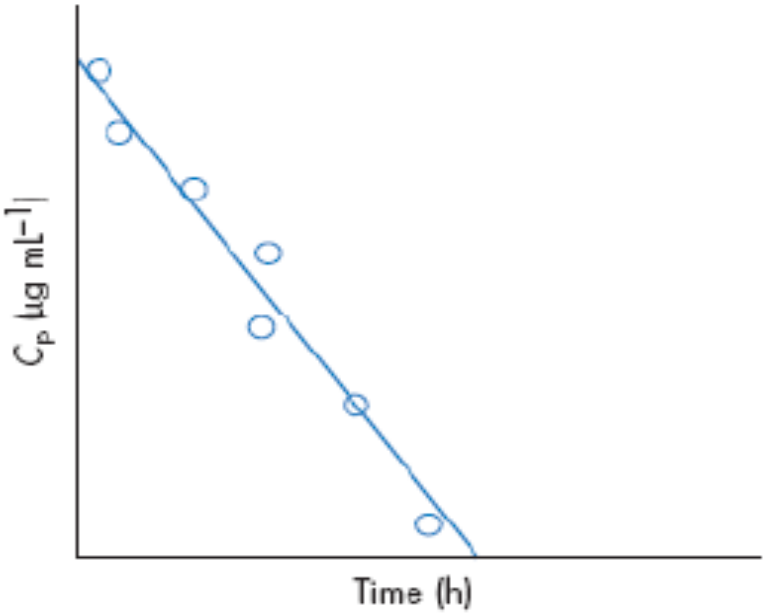
2. The sensitivity of the procedure employed to analyze drug concentration in plasma samples.

   - The low concentration regions may not be detected when using assays with poor sensitivity

3. The physicochemical properties (e.g., the lipophilicity) of a drug.

I.V. bolus administration: One-compartment model



A semilogarithmic plot of (C_p vs t) data for a drug administered as an I.V. bolus dose.

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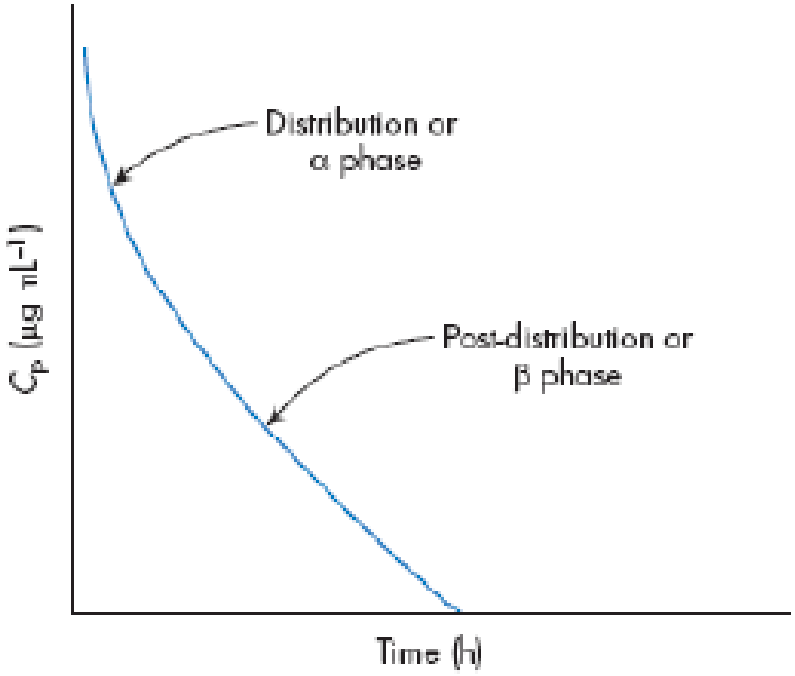
- The plotted curve is a straight line, which clearly indicates the presence of a single pharmacokinetic phase (namely, the elimination phase.)

- These data can be accurately and adequately described by employing the following mono-exponential equation:

$$C = C_o e^{-Kt}$$

where C is the plasma drug concentration at any time t; and C_o is the plasma drug concentration at time t=0.

I.V. bolus administration: Two-compartment model



- Two phases in the (C_p vs t) data.
- The first phase (curvilinear portion) represents drug distribution in the body; and only after a finite time do we see a straight line.
- The time at which the plot begins to become a straight line represents the occurrence of distribution equilibrium.

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- The drug is being distributed slowly and requires a two compartment model for accurate characterization.

- The equation employed to characterize these (C_p vs t) data will be biexponential:

$$C = Ae^{-\alpha t} + Be^{-\beta t}$$

where A and α are parameters associated with drug distribution and B and β are parameters associated with drug post distribution phase.

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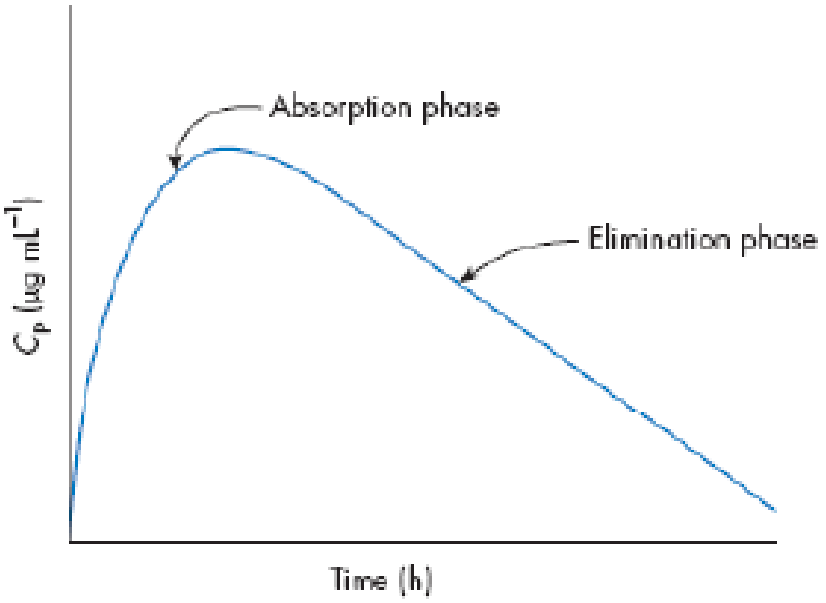
Extravascular administration: One-compartment model



Semilog (C_p vs t) profile representing a one-compartment model for a drug administered extravascularly.

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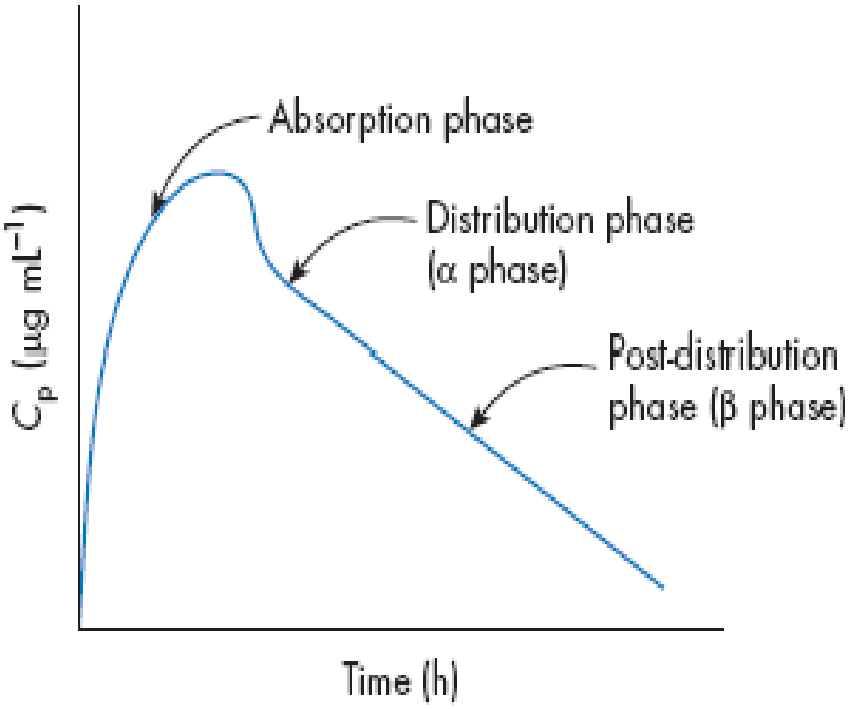
- There are two phases in the profile: absorption and elimination, but only one phase in the post-absorption period.
  - Since the profile contains only one phase in the post-absorption period, these data can be described accurately and adequately by employing a one-compartment model.
  - However, a biexponential equation would be needed to characterize the (C_p vs t) data accurately.

$$C = \frac{K_a F X_o}{V(K_a - K)}(e^{-Kt} - e^{-K_a t})$$

Extravascular administration: Two-compartment model



- Three phases in the (C_p vs t) data for a drug administered by extravascular route.
- These data can be described accurately by employing a two compartment model and the equation will contain three exponential terms.

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- Compartment models are subdivided into:
  - **Mammillary model**
  - **Caternary model**

Mammillary model

- The mammillary model is the most common compartment model used in pharmacokinetics.
- **The model consists of one or more peripheral compartments connected to a central compartment.**
- The drug introduced into a compartment reaches central compartment and from there it distributes to all other compartments connected to it.

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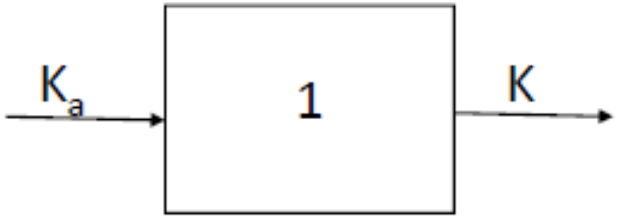
- Model 1. One-compartment open model, IV injection

- Model 2. One-compartment open model with first-order absorption



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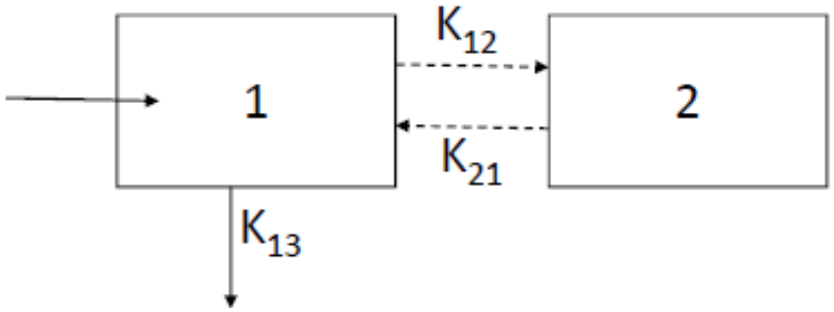
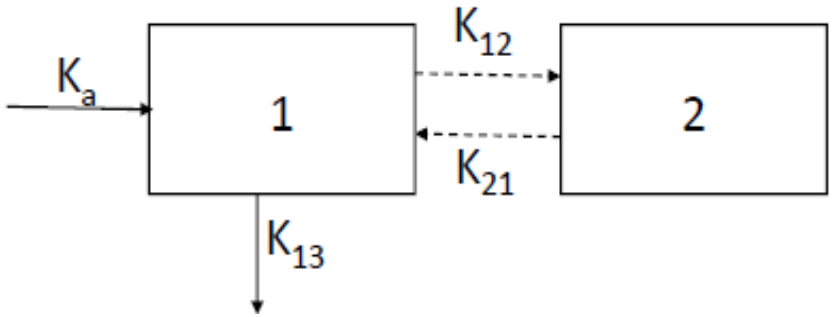
- Model 3. Two-compartment open model, IV injection



- Model 4. Two-compartment open model with first order absorption



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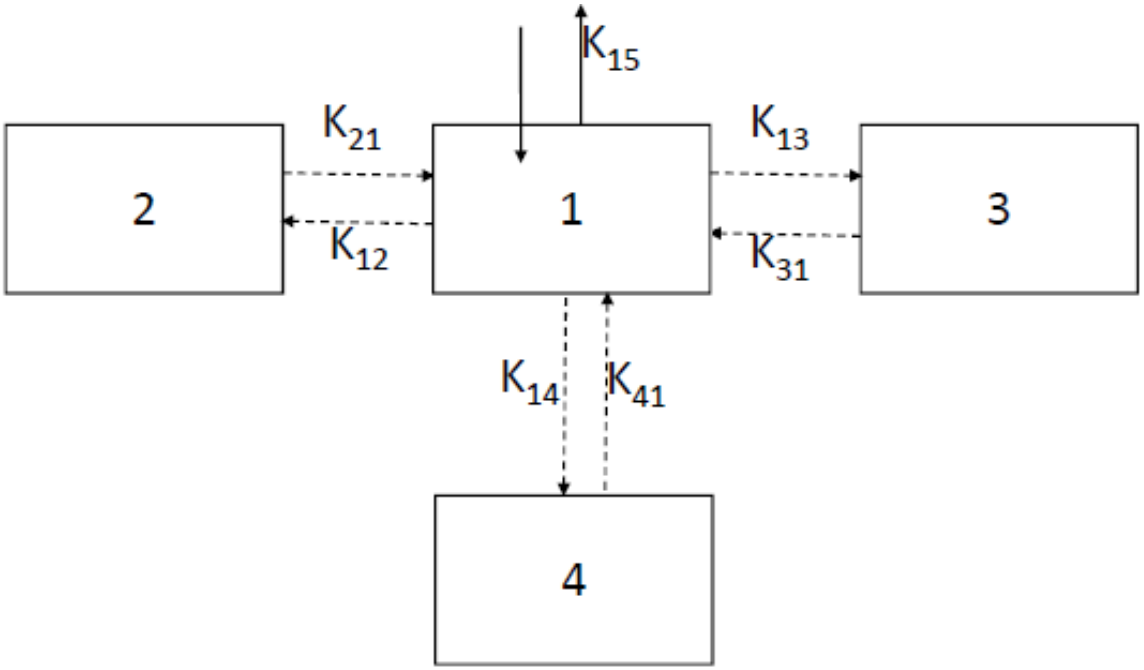
- Model 5. Multi-compartment open model, IV injection



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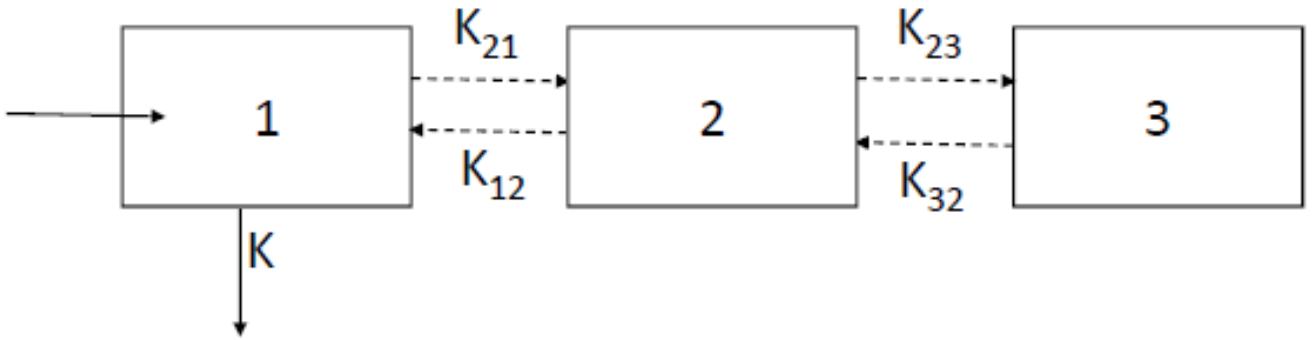
- The drawing of models
  - Gives a visual representation of the rate processes involved,
  - Shows how many pharmacokinetic rate constants are necessary to describe the process adequately, and
  - Enables the pharmacokineticist to develop differential equations to describe drug concentration changes in each compartment.

Caternary Models

- The caternary model consists of compartments joined to one another in a row like the compartments of a train.



Physiologic Model

- Physiologic models, also known as blood flow or perfusion models are pharmacokinetic models based on known anatomic and physiologic data.
- Consideration ~ the blood flow is responsible for distributing a drug to various parts of the body.
- Uptake of a drug into organs is determined by binding of the drug in these tissues.

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- In contrast to the tissue volume of distribution, the actual tissue volume is used.
- Because there are many tissue organs in the body, each tissue volume must be estimated and its drug concentration described.
- The model would potentially predict a realistic tissue drug concentration, which a compartment model fails to do.

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- Major differences between compartmental and physiologic models are:

1. No data fitting is required in the perfusion model.

2. Blood flow, tissue size, and the drug tissue-blood ratio may vary due to certain pathophysiologic conditions.

3. Physiologically based PK models can be applied to several species

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- A physiologic PK model does provide a much better insight of how physiologic factors may change drug distribution from one animal species to another.

- To date, numerous drugs (including digoxin, lidocaine, methotrexate, and thiopental) have been described with perfusion models.

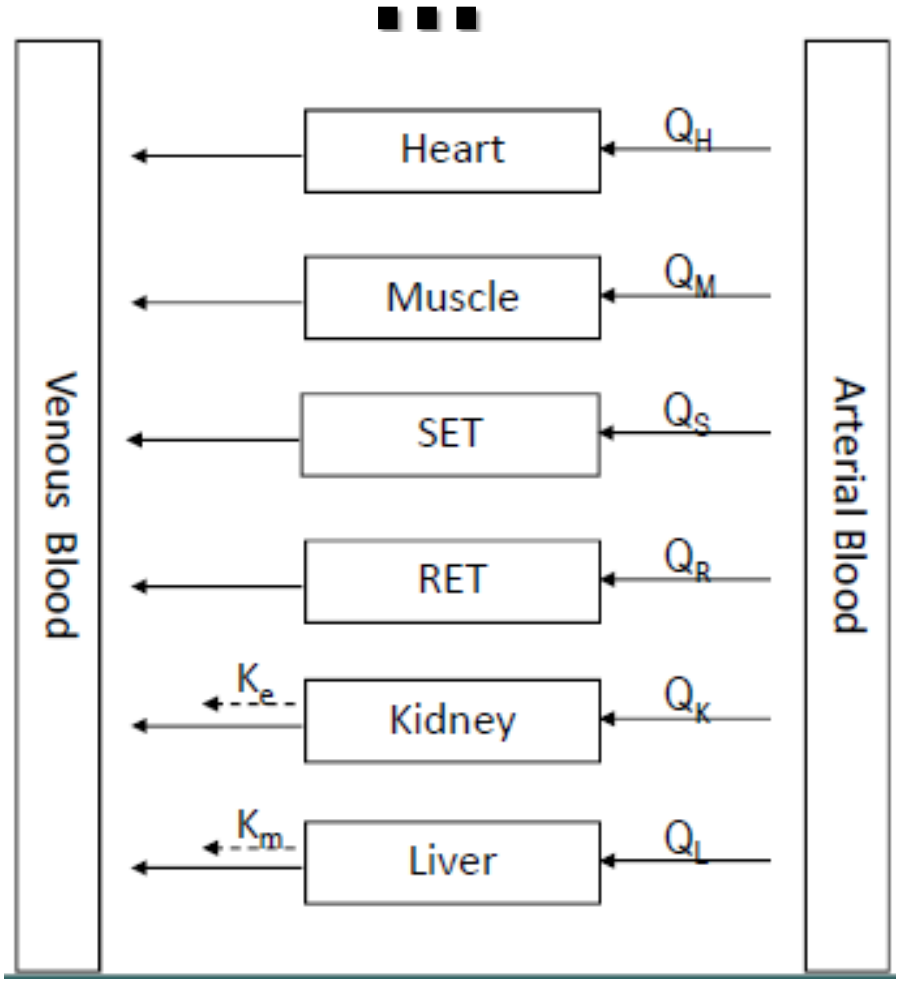

Fig. Schematic representation of perfusion model.

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- The number of tissue compartments in a perfusion model varies from drug to drug.
    - Typically, the tissues or organs that have no drug penetration are excluded from consideration.
    - Such organs as the brain, the bones, or other parts of the central nervous system are often excluded, as most drugs have little penetration into these organs.
- For simplification, tissues with similar blood perfusion properties into a single entity.

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- To describe each organ separately with a differential equation would make the model very complex and mathematically difficult.

- A simpler but equally good approach is to group all the tissues with similar blood perfusion properties into a single entity.

- The real significance of a physiologically based model is the potential application of this model in the prediction of human pharmacokinetics from animal data.

Model-independent PK

- A PK analysis of (C_p vs t) data using compartment models involves application of mathematical equations developed based on a set of assumptions.
- Non-compartmental methods don't need such assumptions.
  - Consequently, sophisticated, and often complex, computational methods are not required.
- Non-compartmental methods for calculating absorption, distribution, and elimination parameters are based on the **theory of statistical moments**.

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- Statistical moments theory provides a unique way to study time-related changes in drug concentration in plasma and/or tissues.
  - The zero moment of drug concentration in (C_p vs t) curve is the total area under the curve from time zero to infinity (AUC_o^∞).
  - The first moment of a plasma drug concentration-time profile is the total area under the curve resulting from a plot of the product of drug concentration and time versus time ($AUMC_o^\infty$).
- Various pharmacokinetic parameters are calculated from the above values.